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(54) Title: RETINOID RELATED MOLECULES FOR THE TREATMENT OF NON-INSULIN DEPENDENT DIABETES MELLITUS

(57) Abstract

Methods for treating and/or preventing non-insulin dependent diabetes mellitus (NIDDM) in subjects having or at substantial risk of developing NIDDM, using specific retinoid compounds that are structurally related to 9-cis retinoid acid which induce the differentiation of preadipocytes into adipocytes, are provided. These compounds may be administered alone or in combination with other anti-diabetogenic agents such as thiazolidinediones.

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RETINOID RELATED MOLECULES FOR THE TREATMENT OF NON-INSULIN DEPENDENT DIABETES MELLITUS

TECHNICAL FIELD OF THE INVENTION

The present invention relates to the discovery that certain retinoid related compounds which are structurally related to 9-cis retinoic acid effectively induce the differentiation of preadipocytes to adipocytes. These compounds, and compositions containing, are useful for the treatment and/or prevention of non-insulin dependent diabetes mellitus (NIDDM).

BACKGROUND OF THE INVENTION

Approximately 3 of 100 persons suffer with diabetes. Of these persons, a large proportion thereof, about 90-95% of the approximately 6 million persons diagnosed with diabetes in the United States, comprise non-insulin dependent diabetes mellitus (NIDDM) or type II diabetes.

NIDDM is characterized by insulin resistance and abnormalities relating to insulin secretion and action. More specifically, NIDDM is characterized by hyperglycemia, the result of insulin resistance in peripheral tissue (skeletal muscle and adipose tissue), which occurs because insulin-stimulated uptake/utilization of glucose is blunted therein; and in the liver, which occurs because insulin suppression of glucose output is insufficient. These impairments in insulin action play an important role in the development of elevated fasting blood glucose and glucose intolerance.

Currently, methods for NIDDM treatments and prevention include diet and exercise (since NIDDM and insulin resistance strongly correlates with

obesity). Also, the oral administration of hypoglycemic drugs to control blood glucose levels is another means of treating NIDDM. Such hypoglycemic agents include insulin and sulfonylurea-containing formations. However, these therapies suffer from significant disadvantages, in particular, the occurrence of potentially life-threatening hypoglycemia which is attributable to hyperinsulinemia. This is problematic as hypoglycemia is associated with an elevated risk of cardiovascular disease, the major killer of diabetics. Therefore, providing a method of treating diabetes that does not increase circulatory insulin concentrations would be highly beneficial.

Recently, a new class of synthetic drugs was identified, thiazolidinediones (TZDs), which drugs have been shown to increase sensitivity to insulin in patients that are resistant to this hormone. Thiazolidinediones reportedly ameliorate insulin-resistance and normalize plasma glucose and insulin (where elevated) without causing a hypoglycemic state, even when administered at very high dosages. The TZD insulin sensitizers, e.g., ciglitazone, englitazone, pioglitazone, BRL 49653 (5-[(4-(2-(methyl-2-pyridinylamino)-ethoxy]phenyl]methyl]-2,4-thiazolidinedione) and troglitazone, enhance insulin-mediated suppression of hepatic glucose output and insulin-stimulated glucose uptake and utilization by adipose tissue. Also, TZDs have been reported to alter glucose transporter (e.g. Glut 4) expression which contributes to increased insulin responsiveness.

One specific TZD member, troglitazone, was recently reported to be effective against NIDDM in a phase III clinical trial (Nolan et al, *N. Engl. J. Med.*, 331:1188-1193, 1994). The potency of TZDs as effective anti-diabetic agents closely matches that adipogenic action, i.e. their ability to differentiate preadipocytes into adipocytes (Harris and Kletzien, *Mol. Pharmacol.*, 45:439-

445, 1994; Wilson et al, *J. Med. Chem.*, 39:665-668, 1996). Also, TZDs have been reported to convert myogenic cells into adipocyte-like cells (Teboul et al, *J. Biol. Chem.*, 270:28183-28187, 1995).

At the molecular level, TZDs have been shown to function as regulators of the nuclear receptor PPARγ (Lehmann et al, *J. Biol. Chem.*, 270:12953-12956, 1995) which is known to play an important role in adipogenesis (Spiegelman and Flier, *Cell*, 87:377-389, 1996; Tontonoz and Spiegelman, *Cell*, 79:1147-1156, 1994). However, the exact cellular mechanism by which TZDs increase insulin sensitivity in NIDDM is not clearly understood. Moreover, a major problem of TZDs is their *in vivo* toxic side effects.

Very recently, PCT application WO 97/10819 (published on March 27, 1997, after the priority date of this application) disclosed that certain types of retinoids, i.e., RXR agonists, when administered alone or in combination with PPARγ agonists such as thiazolidinedione compounds, could be used to treat NIDDM. However, the specific retinoids of the present invention are not mentioned therein.

BRIEF DESCRIPTION OF THE INVENTION

The present invention relates to the discovery that specific retinoid-related molecules, which do not exhibit typical retinoid activities, may be used as therapeutics. These compounds, unlike normal retinoids, exhibit reduced or no ability to induce the differentiation of F9 teratocarcinoma cells or P12 pluripotent teratocarcinoma cells. However, these compounds very potently potentially induce the differentiation of preadipocytes to adipocytes. This property, coupled with the fact that these molecules are well tolerated in

vivo, i.e., they do not exhibit typical retinoid toxicities, renders them well suited for use in the treatment and/or prevention of NIDDM.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 compares the ability of various retinoids according to the invention to induce the differentiation of preadipocytes to adipocytes at different concentrations.

Figure 2 compares the ability of various retinoids according to the invention to induce the differentiation of preadipocytes to adipocytes over a seven day time period.

OBJECTS OF THE INVENTION

It is an object of the invention to provide novel and improved methods for treating and/or preventing NIDDM.

It is a more specific object of the invention to use specific retinoid-related molecules structurally related to 9-cis retinoic acid, which induce the differentiation of preadipocytes to adipocytes, for the treatment and/or prevention of NIDDM.

It is another specific object of the invention to provide novel compositions adopted for the treatment or prevention of NIDDM that comprise the combination of at least one retinoid-related molecule structurally related to 9-cis retinoic acid, which molecule induces the differentiation of preadipocytes to adipocytes and at least one triazolidinedione (TZD) compound.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is based on the discovery that certain retinoid-type molecules, which do not exhibit typical retinoid activities, exhibit the ability to induce differentiation of preadipocytes to adipocytes. Also, these molecules do not exhibit adverse side effects *in vivo*. This adipogenic action renders these compounds, and isomers or pharmaceutically acceptable salts thereof, well suited for the treatment or prevention of NIDDM. In particular, these compounds should exhibit an effective anti-diabetogenic action based on their adipogenic activity, similar to TZDs. However, unlike TZDs, these retinoid compounds should not exhibit toxic side effects upon *in vivo* administration because these molecules do not exhibit typical retinoid toxicities and have been shown to be well tolerated in an animals.

The retinoid-like molecules reported herein are disclosed in U.S. Serial No. 08/429,0096, filed April 26, 1995, now allowed. This application further describes methods for synthesis thereof.

More specifically, it has been surprisingly discovered that the following retinoid compounds effectively induce the differentiation of preadipocytes to adipocytes:

6-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphtylthio)nicotinic acid (referred to in the Examples as C1) (Compound 1);

4-(3-ethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyloxy) benzoic acid (referred to in the Examples, as C2) (Compound 2);

4-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthylthio)benzoic acid (referred to in the Examples as C3) (Compound 3);

4-(3-isopropyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyloxy)benzoic acid (Compound 4);

4-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylthio)benzoic acid

(Compound 5);

4-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyloxy)benzoic acid (Compound 6);

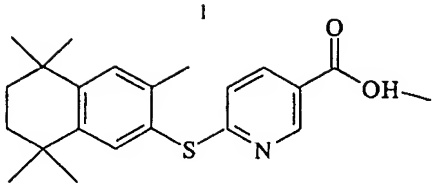
4-(3-bromo-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyloxy)benzoic acid (Compound 7);

3-methyl-4-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphtylthio)benzoic acid (Compound 8); and

3-methyl-4-(3-ethyl-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyloxy)benzoic acid (Compound 9).

The structures for the above-identified retinoid related molecules, identified as Compounds 1-9, are set forth on the following page.

1



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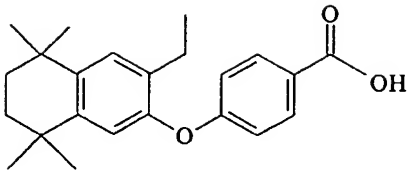

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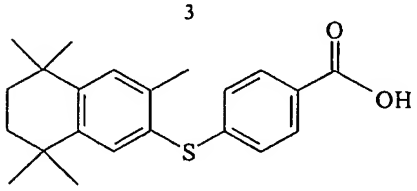

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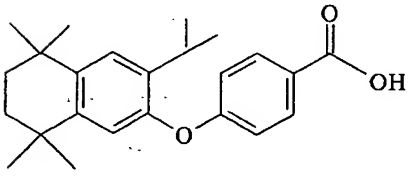

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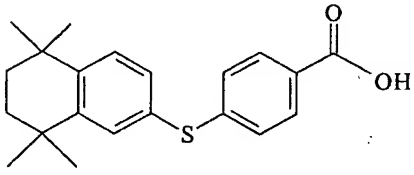

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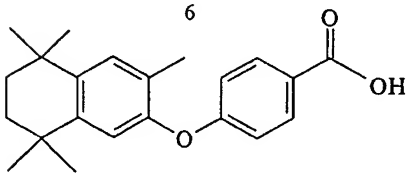

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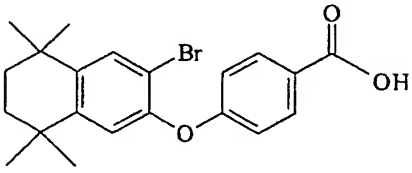

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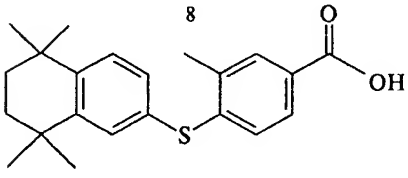

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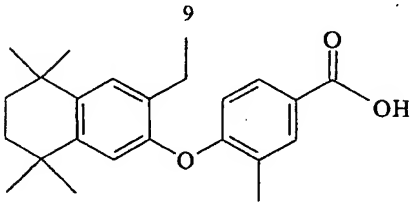

As discussed above, and shown in the Examples which follow, these compounds effectively promote adipogenesis. Therefore, these compounds or isomers or pharmaceutically acceptable salts thereof may be used for the treatment and/or prevention of NIDDM.

In using the subject compounds to treat and/or prevent NIDDM, a therapeutic/prophylactic composition which comprises a therapeutically or prophylactically effective amount of at least one compound according to the invention will be administered to a subject having or at risk of developing NIDDM.

Such pharmaceutical/therapeutic compositions will comprise a vehicle, carrier or diluent which is pharmaceutically acceptable and compatible with the mode of regime of administration selected for the given composition, and a therapeutically or prophylactically effective amount of at least one compound according to the invention, or a pharmaceutically acceptable salt or isomer thereof.

The administration of the compounds according to the invention can be carried out by any suitable means, e.g., systemically, enterally, parenterally, topically or ocularly. However, oral administration is generally preferred.

For enteral administration, the medicinal/pharmaceutical compositions may be in the form of tablets, gelatin capsules, sugar-coated tablets, syrups, suspensions, elixirs, solutions, powders, granules, emulsions, microspheres or nanospheres or lipid or polymeric vesicles which permit a controlled release. For parenteral administration, the compositions may be in the form of solutions or suspensions for perfusion or for injection.

The compounds according to the invention are generally administered at a daily dose of about 0.1 mg/kg to 100 mg/kg of body weight which are administered at the rate of 1 to 3 doses per diem.

For topical administration, the pharmaceutically compositions based on compounds according to the invention may be provided in the form of ointments, creams, milks, pommades, powders, salves, impregnated pads, solutions, gels, sprays, lotions or suspensions. They may also be provided in the form of microspheres or nanospheres or lipid or polymeric vesicles or polymeric patches and hydrogels which permit for controlled release. These compositions for topical administration may, moreover, be provided either in anhydrous form or in an aqueous form. For ocular administration, they are principally eye washes.

These compositions for topical or ocular application contain at least one compound according to the invention or one of its salts, at a concentration preferably ranging from 0.001% to 5% by weight relative to the total weight of the composition.

The medicinal compositions according to the invention may, in addition, contain inert or pharmacodynamically active additives. In particular, the compositions according to the invention may comprise other drugs which are suitable for treating or preventing NIDDM.

In a preferred embodiment, the therapeutic/prophylactic compositions of the invention will comprise at least one retinoid compound according to the invention, in combination with at least one thiazolidinedione compound such as ciglitazone, englitazone, pioglitazone, BRL 49653 (5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]2-4-thiazolidinedione, and troglitazone. The combination of these adipogenic agents should provide at

least the additive and potentially synergistic effects on adipogenic activity. Also, the subject therapeutic or prophylactic compositions may further comprise other drugs useful for the treatment or prevention of diabetes.

The retinoid compounds of the present invention as noted, will preferably be used to treat persons already diagnosed with NIDDM, i.e., who exhibit an active disease condition. However, another important application of the present invention comprises the use of the subject retinoid compounds for the prevention of NIDDM in persons who are at substantial risk of developing diabetes, e.g. because of genetic and/or other risk factors. Such risk factors include, by way of example, obesity, and pancreatic transplant. Also, these compounds or pharmaceutically acceptable salts thereof may be used or for treating persons who exhibit the early, i.e., preclinical signs of NIDDM. Methods for identifying persons who exhibit the early signs of NIDDM or who are at substantial risk of developing NIDDM are known in the diabetic art, and include measuring glucose levels.

In order to further illustrate the present invention and the advantages thereof, the following specific examples are given, it being understood that same are intended only as illustrative and in nowise limitative.

EXAMPLE 1

Effects of Subject Compounds at Different Concentrations on Adipogenesis Activity

3T3-L1 preadipocyte cells (ATCC) were seeded at $5x10^4$ cells per well in DMEM and 10% calf serum in 24 well tissue culture plates. Two days after reaching confluence, differentiation was induced by the addition of different compounds according to the invention as well as suitable control

compounds in DMEM containing 10% fetal calf serum. Media and compounds were changed every three days. Cells were fixed after 7 days post-confluency and the accumulation of lipid droplets in the cytoplasm was determined by oil red O staining.

All cells, including the control cells (vehicle), were treated with the same volume of dimethyl sulfoxide (DMSO), at a level which did not exceed 0.2% final solvent concentration.

All-trans RA (tRA) and 9-cis RA (9cRA) were used as the controls compounds.

Oil red O staining: Seven days post confluency, the cells were washed twice with PBS, fixed at 10% formalin and washed one more time with PBS. Cells were then stained with 60% Oil Red O solution for 30 minutes. Cells were then washed twice with water for 15 minutes each. The Oil Red O stock solution was prepared from 0.5 g Oil Red O dissolved in 100 ml isopropanol and it was filtered prior dilution in PBS to render 60% Oil Red O solution.

The results of these experiments are contained in Figure 1. These results establish that the compounds of the inventors induced differentiation of preadipocytes into adipocytes. By contrast, the control compounds did not exhibit similar activity. Moreover, the results indicate that such differentiation was induced in a concentration-dependent manner.

EXAMPLE II

Effects of Subject Compounds on Adipogenesis Over Time

3T3-L1 preadipocyte cells (ATCC) were seeded at $5x10^4$ cells per well in DMEM and 10% calf serum in 24 well tissue culture plates. Two days

after reaching confluence, differentiation was induced by addition of the different compounds according to the invention in DMEM containing 10% fetal calf serum (Day 0). Media and compounds were changed every three days. Cells were fixed at the indicated days and processed as explained in Example I.

All cells, including control cells (vehicle), were treated with the same volume of dimethyl sulfoxide (DMSO) never exceeding 0.2% final solvent concentration.

As a positive control for differentiation, cells were treated with 10 μg insulin per ml and 1 μM dexamethasone (Ins/Dex). 1μM All-trans RA (tRA) and 2 μM 9-cis RA (9cRA) were used as additional controls.

C1, C2 and C3 were used at a final concentration of 1 μM.

The results of these experiments are contained in Figure 2. These results show that the compounds according to the invention induced differentiation of preadipocytes into adipocytes in a time dependent manner. By contrast, the control compounds, insulin, dexmethasone, all-trans RA and 9-cis RA did not exhibit similar activity.

Therefor, the results obtained substantiate that the compounds of the invention effectively induce adipogenesis in a time and concentration-dependent manner. Accordingly, they should provide effective therapeutic and/or prophylactic agents for treating and/or preventing NIDDM in subjects in need of such treatment.

CLAIMS

1. A method of treating and/or preventing non-insulin dependent diabetes mellitus (NIDDM) in a subject having or at substantial risk of developing NIDDM, comprising administering a prophylactically or therapeutically effective amount of at least one compound selected from the group consisting of:

6-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphtylthio)nicotinic acid;

4-(3-ethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyloxy) benzoic acid;

4-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthylthio)benzoic acid;

4-(3-isopropyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyloxy)benzoic acid;

4-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylthio)benzoic acid;

4-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyloxy)benzoic acid;

4-(3-bromo-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyloxy)benzoic acid;

3-methyl-4-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphtylthio)benzoic acid;

3-methyl-4-(3-ethyl-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyloxy)benzoic acid;

or a pharmaceutically acceptable salt thereof.

2. The method of Claim 1, wherein the method further comprises administering at least one other anti-diabetogenic agent.

3. The method of Claim 2, wherein said other anti-diabetogenic agent is a thiazolidinedione.

4. The method of Claim 3, wherein said compound is selected from the group consisting of ciglitazone, englitazone, pioglitazone, (5-[[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedone) and troglitazone.

5. The method of Claim 1, wherein said compound is administered systemically, enterally, parenterally, topically or ocularly.

6. The method of Claim 1, wherein the compound is administered orally.

7. The method of Claim 1, wherein said compound is contained in a pharmaceutically acceptable form selected from the group consisting of tablets, gelatin capsules, sugar-coated tablets, syrups, elixirs, solutions, powders, granules, emulsions, microspheres, nanospheres, lipid or polymeric vesicles that provide for controlled release, ointments, creams, milks, pommades, powders, salves, impregnated pads, gels, sprays, lotions and suspensions.

8. The method of Claim 1, wherein the compound is administered daily at a dose of about 0.01 mg/kg to 100 mg/kg of body weight, at a rate of about 1 to 3 doses per diem.

9. The method of Claim 1, which is administered to a subject at substantial risk of developing NIDDM because of genetic and/or other risk factors.

10. The method of Claim 9, wherein the subject is a person at risk of developing recurrent type II diabetes.

11. The method of Claim 1, wherein the compound is administered by injection.

12. A composition adopted for the treatment and/or prevention of non-insulin dependent diabetes mellitus (NIDDM) that comprises the combination of:

(i) at least one retinoid-related compound selected from the group consisting of

6-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphtylthio)nicotinic acid;

4-(3-ethyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyloxy) benzoic acid;

4-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthylthio)benzoic acid;

4-(3-isopropyl-5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyloxy)benzoic acid;

4-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylthio)benzoic acid;

4-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyloxy)benzoic acid;

4-(3-bromo-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyloxy)benzoic acid;

3-methyl-4-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphtylthio)benzoic acid;

3-methyl-4-(3-ethyl-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyloxy)benzoic acid;

or a pharmaceutically acceptable salt thereof;

(ii) at least one thiazolidinedione compound; and

(iii) a pharmaceutically acceptable carrier or excipient.

13. The composition of Claim 12, wherein said thiazolidinedione compound is selected from the group consisting of ciglitazone, englitazone, pioglitazone, (5-[4-[2-(methyl-2-pyridinylamino)ethoxy]phenyl]methyl]-2,4-thiazolidinedione and troglitazone.

14. The composition of Claim 12, which is adopted for oral administration.

15. The composition of Claim 14, which is in a form selected from the group consisting of tablets, gelatin capsules, sugar-coated tablets, syrups, elixirs, solutions, powders, granules, emulsions, microspheres, nanospheres, lipid or polymeric vesicles that provide for controlled release, ointments, creams, milks, pommades, powders, salves, impregnated pads, gels, sprays, lotions and suspensions.

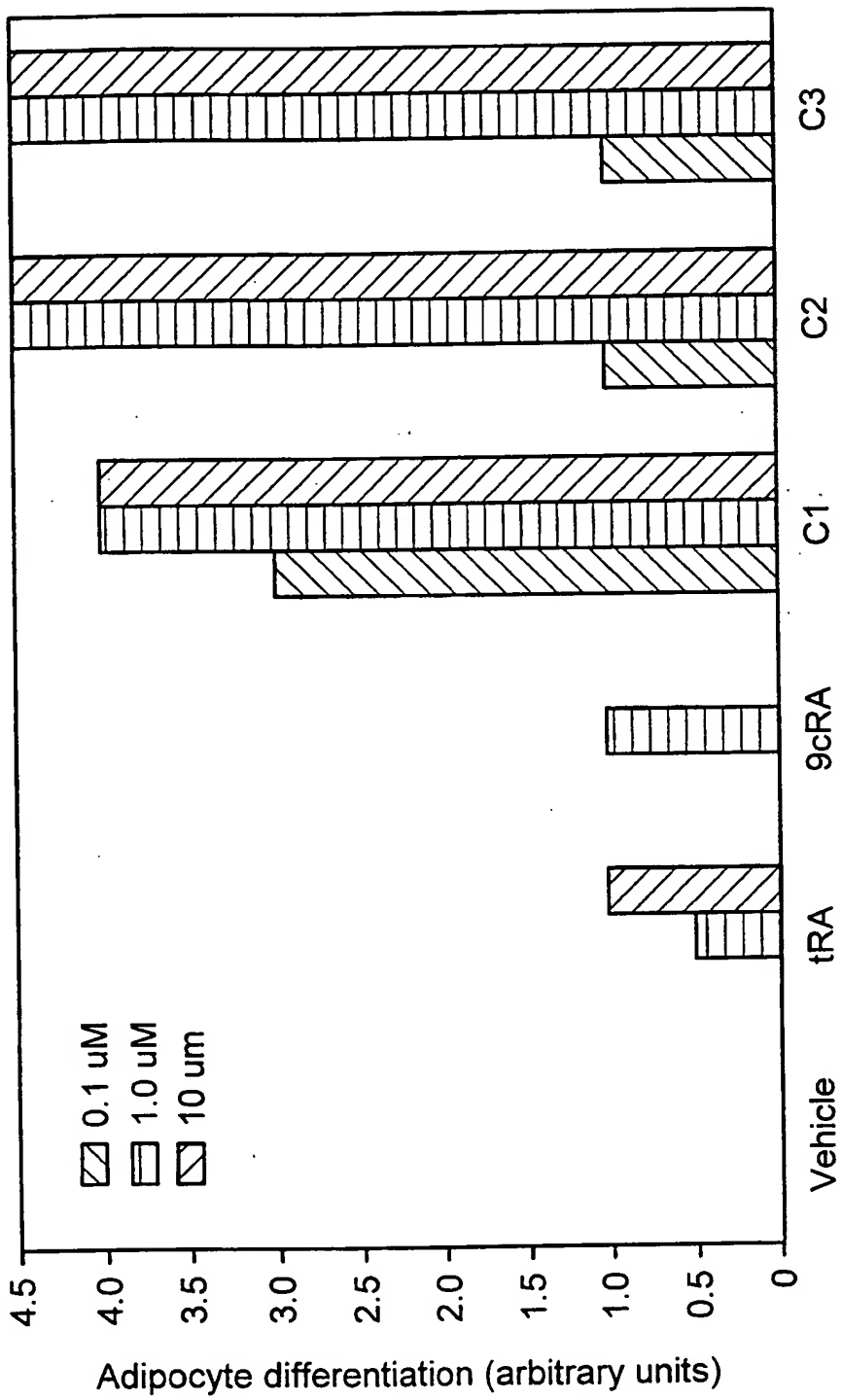
C3
C2
C1
9cRA
tRA
Vehicle
0.1 uM
1.0 uM
10 um
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Adipocyte differentiation (arbitrary units)

FIG. 1

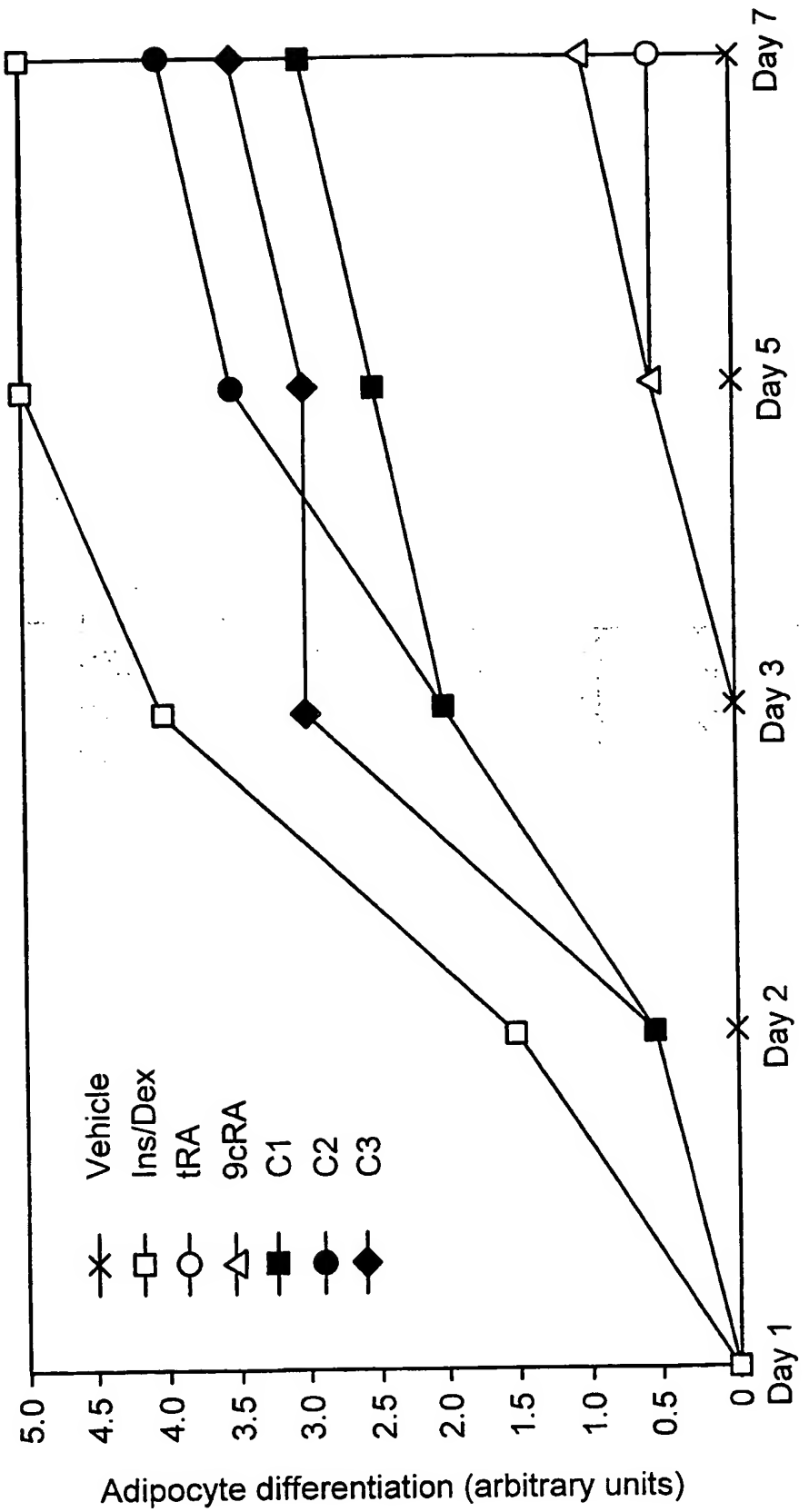
Adipocyte differentiation (arbitrary units)
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Day 1
Day 2
Day 3
Day 5
Day 7
Vehicle
Ins/Dex
tRA
9cRA
C1
C2
C3

FIG. 2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/05591

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :A61K 31/44, 31/19
US CL :514/356, 570
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/356, 570

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,560,908 A (SATOH et al.) 01 October 1996.	1-15
A	US 5,478,852 A (OLEFSKY et al.) 26 December 1995.	1-15
A	US 5,470,879 A (SAUVAIRE et al.) 28 November 1995.	1-15
A	US 5,444,086 A (MALAMAS) 22 August 1995.	1-15
A	US 5,124,360 A (LARNER et al.) 23 June 1992.	1-15

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 19 APRIL 1998	Date of mailing of the international search report 08 JUL 1998
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer RAYMOND J. HENLEY III Telephone No. (703) 308-1235

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